Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 3

B. In the Claims

Please amend claims 37, 42 to 45 and 56 without prejudice.

Upon entry of the present amendment, the claims will stand as follows in the present application:

1. (original) A compound having the structure (I):

$$R_1$$
 R_2
 R_3
 R_3

wherein:

R₁ is an alkyl;

R₂ is a substitutent selected from a group consisting of hydrogen, an alkyl, halogen, and an alkoxy group; and

R₃ is a substitutent selected from a group consisting of an unsubstituted or substituted alkyl group, halogen, an alkoxy group, acetyl group, and nitro group,

or a pharmaceutically acceptable salt thereof.

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 4

2. (original) The compound of claim 1, wherein:

 R_1 is selected from a group consisting of ethyl, n-propyl and n-amyl;

R₂ is selected from a group consisting of hydrogen, chlorine, methyl, and methoxy;

 R_3 is selected from a group consisting of methyl, chlorine, iodine, trifluoromethyl, and methoxy.

3. (original) The compound of claim 1, wherein the compound having the structure (I) is selected from the group of compounds having the formulae (1)-(7):

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 5

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 6

$$H_2C$$
 H_2C
 CH_3
 CH_3
 CH_3

4. (original) A compound having structure (II):

$$R_4$$
 C
 NH
 O
 NH
 O
 OCH_3
 OCH_3

wherein:

R₄ is selected from a group consisting of tert-butyl and chlorine; and

R₅ is selected from a group consisting of nitro group and bromine,

or a pharmaceutically acceptable salt thereof.

5. (original) The compound of claim 4, wherein the compound having structure (II) is selected from a group consisting of compounds having the formulae (8) and (9):

PATENT Beachy et al. Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 7

(original) A compound having the structure (III): 6.

$$S$$
 CH_2
 CH_3
 CH_3
 CH_3

wherein:

R₆ is selected from a group consisting of methyl and ethoxy group; and

R₇ is selected from a group consisting of hydrogen and methyl,

or a pharmaceutically acceptable salt thereof.

Attorney Docket No.: JHU1920-1

PATENT

Beachy et al.

Application No.: Not Yet Assigned
US Submission Date: March 29, 2006

Based on Intl Appl: PCT/US2004/032482
IA Filing Date: September 29, 2004

Page 8

7. (original) The compound of claim 6, wherein the compound having the structure (III) is selected from the group of compounds having the formulae (10) and (11):

$$S$$
 CH_2
 CH_3

(10)

(11)

8. (original) A compound having the structure (IV):

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 9

$$\begin{array}{c} R_{8} \\ R_{9} \end{array}$$

wherein:

R₈ is selected from a group consisting of hydrogen and methyl;

R₉ is selected from a group consisting of hydrogen, chlorine and fluorine;

X is selected from a group consisting of ethyl and fluorophenyl; and

Y is selected from a group consisting of oxygen and sulfur,

or a pharmaceutically acceptable salt thereof.

9. (original) The compound of claim 8, wherein the compound having the structure (IV) is selected from the group of compounds having the formulae (12)-(15):

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 10

(13)

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & &$$

(14)

PATENT Beachy et al. Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 11

(original) A compound having the structure (V): 10.

wherein Het is a heterocyclic radical.

- 11. (original) The compound of claim 10, wherein the heterocyclic radical is selected from a group consisting of pyridyl and thiazolyl.
- 12. (original) The compound of claim 10, wherein the compound having the structure (V) is selected from the group of compounds having the formulae (16) and (17):

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 12

13. (original) A compound having the structure (VI):

wherein:

Ar₁ is an aromatic substitutent selected from a group consisting of

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 13

Ar₂ is an aromatic substitutent having the structure:

R₁₀ is selected from a group consisting of methyl and chlorine;

R₁₁ is selected from a group consisting of hydrogen, methyl, and chlorine; and

R₁₂ is selected from a group consisting of hydrogen,

or a pharmaceutically acceptable salt thereof.

14. (original) The compound of claim 13, wherein the compound having the structure (VI) is selected from the group of compounds having the formulae (18)-(24):

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 14

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 15

(22)

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 16

15. (original) A compound having the structure (VII):

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 17

wherein:

R₁₃ is selected from a group consisting of chlorine, bromine, and methoxy; and

Z is oxygen or a single σ -bond,

or a pharmaceutically acceptable salt thereof.

16. (original) The compound of claim 15, wherein the compound having the structure (VII) is selected from the group of compounds having the formulae (25)-(27):

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 18

(26)

(27)

17. (original) A compound having the structure (VIII):

$$O \longrightarrow C \longrightarrow N \longrightarrow Ar_4$$

$$(VIII)$$

wherein:

Ar₃ is an aromatic substitutent selected from a group consisting of

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 19

Ar₄ is an aromatic substitutent having the structure

R₁₄ is selected from a group consisting of hydrogen and bromine; and

R₁₅ is selected from a group consisting of tert-butyl and iodine,

or a pharmaceutically acceptable salt thereof.

18. (original) The compound of claim 17, wherein the compound having the structure (VIII) is selected from the group of compounds having the formulae (28) and (29):

(28)

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 20

(29)

19. (original) A compound having the structure (IX):

$$R_{16}$$

$$(IX)$$

wherein:

Ar₅ is an aromatic substitutent selected from a group consisting of

$$HN$$
 CI and NH_2 ; and

R₁₆ is selected from a group consisting of hydrogen and methyl,

or a pharmaceutically acceptable salt thereof.

PATENT Beachy et al. Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 21

20. (original) The compound of claim 19, wherein the compound having the structure (IX) is selected from the group of compounds having the formulae (30) and (31):

(30)

$$N_{NH_2}$$
.

(original) A compound having the structure (X): 21.

PATENT Beachy et al. Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 22

wherein:

R₁₇ is selected from a group consisting of hydrogen and methyl; and

 R_{18} is selected from a group consisting of methyl, methoxy, and ethoxy,

or a pharmaceutically acceptable salt thereof.

22. (original) The compound of claim 21, wherein the compound having the structure (X) is selected from the group of compounds having the formulae (32)-(34):

(32)

(33)

Beachy et al.

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 23

PATENT

Attorney Docket No.: JHU1920-1

(34)

23. (original) A compound selected from a group having the formulae (35)-(60):

(35)

(36)

Beachy et al. Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 24

$$(37)$$

$$H_{3}C$$

$$C$$

$$N$$

$$CH_{3}$$

$$(38)$$

$$(38)$$

(39)

PATENT

Beachy et al. Attorney Docket No.: JHU1920-1

PATENT

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 25

(41)

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 26

$$H_3C$$
 H_3C
 H_3C

(44)

(45)

(46)

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 27

$$\begin{array}{c|c} & & & \\ & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ &$$

(48)

(49)

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 28

(50)

(51)

(52)

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 29

(55)

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 30

(57)

(58)

Beachy et al.

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 31

PATENT

Attorney Docket No.: JHU1920-1

24. (original) A compound, comprising an alkylpyridyl moiety bridged to a benzamide moiety, wherein the benzamide moiety includes a first substitutent attached to the benzamide moiety via the nitrogen atom of the benzamide moiety.

(60)

25. (original) The compound of claim 24, wherein the first substitutent comprises an aryl structure which includes at least one second substitutent, wherein the second substitutent is selected from a group consisting of an unsubstituted or unsubstituted alkyl, a halogen, an alkoxy, acetyl, and nitro.

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 32

- 26. (original) A compound, comprising two benzamide moieties connected with a phenylene bridge.
- 27. (original) The compound of claim 26, wherein the phenylene bridge is 1,3-phenylene group.
- 28. (original) The compound of claim 26, wherein each of the benzamide moieties includes a substitutent, wherein the substitutent is selected from a group consisting of *tert*-butyl, chlorine, bromine, and nitro.
- 29. (original) A compound, comprising a first heterocyclic ring fused with a second heterocyclic ring, wherein:
 - (a) the first ring is a substituted 1,3-diazine-6-one; and
- (b) the second ring is selected from an N-substituted thiazole-2-thione and a substituted thiophene.
- 30. (original) A compound, comprising a thiazole moiety carrying a heterocyclic substitutent and a secondary amino substitutent, wherein:
 - (a) the heterocyclic substitutent is elected from thiazolyl and pyridyl; and
 - (b) the secondary amino substitutent is ethoxyphenylene group.
- 31. (original) A compound, comprising a phtalazine moiety carrying at least two substitutents, wherein:
 - (a) the first substitutent includes a substituted phenyl or benzyl group; and
 - (b) the second substitutent includes a secondary aromatic amino group.

Beachy et al. Attorney Docket No.: JHU1920-1

PATENT

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 33

- 32. (original) A compound, comprising a substituted chromone moiety carrying at least two substitutents, wherein:
 - (a) the first substitutent includes a substituted phenyl or phenoxy group; and
 - (b) the second substitutent includes an aromatic ester group.
- 33. (original) A compound, comprising a substituted benzoxazole moiety carrying at least two substitutents, wherein:
 - (a) the first substitutent is selected from a substituted phenyl group and a substituted benzamido group; and
 - (b) the second substitutent is selected from a substituted phenyl group and a substituted furylamido group.
- 34. (original) A compound, comprising a phenylquinazoline moiety and further including a substitutent, wherein the substitutent is selected from a secondary aromatic amino group and an anyline moiety.
- 35. (original) A compound, comprising a thiazole moiety bridged to a substituted pyrrole-pyridine moiety.
- 36. (original) The compound of claim 35, wherein the thiazole moiety further includes a secondary aromatic amino group.
- 37. (currently amended) A method for treating a cell proliferative disorder in a subject, said method comprising administering an effective amount of the compound of claim 1 any compound of claims 1 36, or any combination thereof, or pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual diastereomers thereof, to a subject in need of such treatment.

Beachy et al.

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 34

38. (original) The method of claim 37, wherein the cell proliferative disorder is basal cell carcinoma, medulloblastoma or meningioma.

PATENT

Attorney Docket No.: JHU1920-1

- 39. (original) The method of claim 37, wherein the subject is a human or another mammal.
- 40. (original) The method of claim 37, further including administering the compound in combination with a therapeutic agent, immunomodulatory agent, therapeutic antibody or an enzyme inhibitor.
- 41. (original) The method of claim 40, wherein the therapeutic agent is methotrexate, cisplatin/carboplatin, canbusil, dactinomicin, taxol (paclitaxel), antifolate, colchicine, demecoline, etoposide, taxane/taxol, docetaxel, doxorubicin, anthracycline antibiotic, doxorubicin, daunorubicin, carminomycin, epirubicin, idarubicin, mithoxanthrone, 4-dimethoxy-daunomycin, 11-deoxydaunorubicin, 13-deoxydaunorubicin, adriamycin-14-benzoate, adriamycin-14-octanoate or adriamycin-14-naphthaleneacetate, irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab, trastuzumab, bevacizumab, OSI-774, or Vitaxin.
- 42. (currently amended) A pharmaceutical composition comprising the compound of claim 1 any compound of claims 1 36, or any combination thereof, in a pharmaceutically acceptable carrier.
- 43. (currently amended) An article of manufacture comprising packaging material and a pharmaceutical composition contained within the packaging material, wherein the packaging material comprises a label which indicates that the pharmaceutical composition can be used for treatment of disorders and wherein said pharmaceutical composition

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 35

comprises the compound of claim 1 any compound of claims 1 36, or any combination thereof.

- 44. (currently amended) A process for making a pharmaceutical composition comprising the compound of claim 1 combining any compound of claims 1-36, or any combination thereof, or its pharmaceutically acceptable salts, hydrates, solvates, crystal forms salts and individual diastereomers thereof, and a pharmaceutically acceptable carrier.
- 45. (currently amended) A method of inhibiting an altered growth state of a cell having a *ptc* loss-of-function phenotype, a *hedgehog* gain-of-function phenotype or a *smoothened* gain-of-function phenotype, comprising contacting the cell with a composition comprising the compound of claim 1 any compound of claims 1 36, or any combination thereof.
- 46. (original) The method of claim 45, wherein the compound is a *hedgehog* signal transduction agonist.
- 47. (original) The method of claim 46, wherein the agonist agonizes *ptc* inhibition of *hedgehog* signaling.
- 48. (original) The method of claim 45, wherein the compound is a *hedgehog* signal transduction antagonist.
- 49. (original) The method of claim 48, wherein the antagonist interferes with activation of a *hedgehog*, *patched*, or *smoothened*-mediated signal transduction pathway.
 - 50. (original) The method of claim 45, wherein the cells are normal cells.
 - 51. (original) The method of claim 45, wherein the cells are cancer cells.

PATENT Beachy et al. Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 36

- 52. (original) The method of claim 45, wherein the contacting is performed in vivo.
- 53. (original) The method of claim 45, wherein the contacting is performed in vitro.
- 54. (original) The method of claim 45, wherein the composition is administered as part of a therapeutic or cosmetic application.
- 55. (original) The method of claim 53, wherein the therapeutic or cosmetic application is regulation of neural tissues, bone and cartilage formation and repair, regulation of spermatogenesis, regulation of smooth muscle, regulation of lung, liver and other organs arising from the primitive gut, regulation of hematopoietic function, or regulation of skin and hair growth.
- 56. (currently amended) A method of identifying a compound that modulates cell proliferation in a cell having a ptc loss-of-function phenotype, a hedgehog gain-of-function phenotype or a *smoothened* gain-of-function phenotype, comprising:
 - incubating components comprising the compound of claim lany compound of claims 1-36, a test compound, and a cell having a ptc loss-of-function phenotype, a hedgehog gain-of-function phenotype or a smoothened gain-of-function phenotype, under conditions sufficient to allow the components to interact; and
 - measuring the ability of the test compound to affect cell proliferation by detecting an increase or decrease in expression of signal transduction activity.
- 57. (original) The method of claim 56, wherein the signal transduction activity is expression of hedgehog, ptc, or smoothened.

Beachy et al.

PATENT Attorney Docket No.: JHU1920-1

Application No.: Not Yet Assigned US Submission Date: March 29, 2006 Based on Intl Appl: PCT/US2004/032482

IA Filing Date: September 29, 2004

Page 37

- 58. (original) A method of monitoring a therapeutic regimen for treating a subject having a cell proliferative disorder comprising determining a change in cell proliferation during therapy.
- 59 (original) The method of claim 58, wherein the therapy comprises the treatment of claim 37.